MALLINCKRODT

**Mallinckrodt Inc.** 675 McDonnell Blvd. P.O. Box 5840 St. Louis, MO 63134 Phone: (314) 654-2000 Fax: (314) 654-6496

September 27, 1999

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

## CITIZEN PETITION

Mallinckrodt Inc. submits this petition pursuant to 21 CFR §§10.20 and 10.30, under Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and 21 C.F.R. §314.93 to request that the Commissioner of Food and Drugs make a determination that an Abbreviated New Drug Application may be submitted for Hydrocodone Bitartrate and Acetaminophen Tablets, USP (5 mg/325 mg) which relies on a listed drug that is not being marketed.

### A. Action Requested

The petitioner requests that the Commissioner of Food and Drugs make a determination that an Abbreviated New Drug Application may be submitted per 21 C.F.R. §314.122 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP (5 mg/325 mg) for product that, to the best of Mallinckrodt Inc.'s knowledge, has been determined to be safe and effective, yet has never been marketed.

### B. Statement of Grounds

The basis for this proposed Abbreviated New Drug Application is Lortab 5/325 owned by UCB Pharma, Inc. (ANDA #40-099). However, Lortab 5/325 is not identified as a reference listed drug in the 19th edition of *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) and furthermore, the product is not currently being marketed. The legal basis for UCB's ANDA #40-099 was a Citizen Petition filed by Mikart Inc. (Docket No. 87P-0129/CP) which was approved June 8, 1987 for submission of an Abbreviated New Drug Application for Hydrocodone Bitartrate and Acetaminophen Tablets, USP (5 mg/325 mg). The listed drug product which Mikart referenced in the petition is Vicodin (Hydrocodone Bitartrate and Acetaminophen Tablets, USP 5 mg/500 mg) manufactured by Knoll Pharmaceuticals, Inc. A copy of the June 8, 1987 approval letter as well as a copy of the relevant pages of the Orange Book are attached for your review. Based on the Orange Book, Mikart has not received

99P-4209 CP1

approval to market a 5 mg/325 mg strength of Hydrocodone Bitartrate and Acetaminophen Tablets, USP.

Consistent with Mikart's suitability petition (Docket No. 87P-0129/CP), Mallinckrodt intends to compare its proposed 5 mg/325 mg test product to Vicodin 5 mg/500 mg for dissolution testing. The reference product, Vicodin (Hydrocodone Bitartrate and Acetaminophen Tablets, USP 5 mg/500 mg) is classified AA in the 19th edition of *Approved Drug Products with Therapeutic Equivalence Evaluations*. Mallinckrodt Inc.'s proposed test product (Hydrocodone Bitartrate and Acetaminophen Tablets, USP 5 mg/325 mg), which differs only in formulation and a smaller amount of acetaminophen, would also qualify for an AA rating. Therefore, with acceptable dissolution testing, there would be no need to conduct an *in-vivo* bioequivalence study.

## C. Environmental Impact

An environmental assessment on the action requested in this petition qualifies for a categorical exclusion under 21 CFR 25.31. Therefore, an environmental assessment is not required for the requested action.

## D. Economic Impact

Pursuant to 21 CFR 10.30(b), economic impact information is to be submitted only when requested by the Commissioner. Mallinckrodt Inc. will promptly provide such information if so requested.

## E. Certification

Mallinckrodt Inc. certifies that, to its best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Connie McNabb

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

RECEIVED JUN 1 1 1987

Food and Drug Administration
Rockville MD 20857

JUN 8 1987

Mikart Inc.
Attn: Ms. Cerie B. McDonald
2090 Marietta Boulevard
Atlanta, GA 30318

Docket No. 87P-0129/CP

Dear Ms. McDonald:

This is in response to your petition filed on 4/10/87 requesting permission to file Abbreviated New Drug Applications (ANDAs) for the following drug products acetaminophen (APAP) and Hydrocodone Bitartrate (HCB) 325 mg/2.5 mg, 325 mg/5 mg, 325 mg/7.5 mg and 325 mg/10 mg Tablets. The listed drug product to which you refer is Vicodin (acetaminophen 500 mg and hydrocodone bitartrate 5 mg) Tablets manufactured by Knoll Pharmaceutical. We have reviewed your petition under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (Act), and have determined that it is approved. This letter represents the Agency's determination that ANDAs may be submitted for the above-referenced products.

Your request involves a change in strength of non narcotic component of the listed drug product, i.e. APAP from 500 mg to 325 mg and additional strengths of HCB, i.e. from 5 mg to 2.5 mg, 7.5 mg and 10 strengths. The type of changes you request are the type of changes authorized under Section 505 (j)(2)(C) of the Act.

Under Section 505(j)(2)(C)(i) of the Act the Agency will approve a petition seeking a strength which differs from the strength of the listed drug product unless it finds that investigations must be conducted to show the safety and effectiveness of the differing strength.

The Agency has determined that the change in strength of both the non-narcotic and narcotic components of the proposed products do not pose questions of safety or effectiveness for the reasons discussed below.

The approved labeling for the listed drug provides for dosage adjustment according to the severity of pain and response of the patient. The labeling for the listed drug states that the dose may be adjusted up to two tablets (10 mg of HCB and 1000 mg of APAP) in a single dose. Therefore the dose of the proposed products falls within the dosing range recommended for the listed drug. Despite these facts the Agency would not usually approve a petition to submit an ANDA for a proposed product with a higher or lower strength dosage unit than had been previously approved. However, the Agency has concluded that codeine and HCB have a potency ratio of 6:1. Based upon the 6:1 potency ratio, a proposed product containing a 2.5 mg, 5 mg, 7.5 mg or 10 mg dose of

HCB is equivalent to approved products containing 15 mg, 30 mg, 45 mg and 60 mg of codeine respectively as an initial dose. In addition, there are listed drug products that contain 325 mg of APAP in combination with narcotic analgesics. The Agency has determined that there are no investigations necessary to establish the safety and effectiveness of the change in strength of the proposed products and, therefore, ANDAs may be submitted for these products.

The approval of these petitions to allow ANDAs to be submitted for the above referenced products does not mean that the Agency has determined that ANDAs will be approved for the products. The determination that ANDAs will be approved is not made until the ANDAs themselves are submitted and reviewed by the Agency.

To permit review of your ANDA submissions you must submit all information required under Sections 505(j)(2)(A) and (B) of the Act. To be approved the products will, among other things, be required to meet current bioequivalence requirements under Section 505(j)(2)(A)(iv) of the Act. We suggest that you contact the Director, Division of Bioequivalence at (301) 443-0181 to determine the specific requirements for these products. During the review of your applications, the Agency may require the submission of additional information.

The listed drug product to which you refer in your ANDA must be the one upon which you based these petitions. In addition, you should refer in your ANDA to the appropriate petition docket number cited above, and include a copy of this letter in the ANDA submissions.

A copy of this letter approving your petitions will be placed on public display in the Dockets Management Branch, HFA-305, Room 4-62.

Sincerely yours,

Peter H. Rheinstein, M.D., J.D., M.S.
Director, Office of Drug Standards
Center for Drugs and Biologics

# APPROVED DRUG PRODUCTS
## with
# THERAPEUTIC EQUIVALENCE EVALUATIONS

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This volume and accompanying first supplement are current through January 31, 1999.

## 19TH EDITION

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFORMATION TECHNOLOGY
DIVISION OF DATA MANAGEMENT AND SERVICES

1999

## ACETAMINOPHEN; HYDROCODONE BITARTRATE

TABLET; ORAL
HYDROCODONE BITARTRATE AND ACETAMINOPHEN

| | | | | |
|---|---|---|---|---|
| AA | | VINTAGE PHARMS | 650MG;10MG | N40143 001 FEB 22, 1996 |
| AA | | | 750MG;7.5MG | N40157 001 APR 12, 1996 |
| AA | | WATSON LABS | 500MG;2.5MG | N40123 003 MAR 04, 1996 |
| AA | | | 500MG;2.5MG | N81079 001 AUG 30, 1991 |
| AA | | | 500MG;5MG | N40122 001 MAR 04, 1996 |
| AA | | | 500MG;5MG | N89883 001 DEC 01, 1988 |
| AA | | | 500MG;7.5MG | N40123 004 MAR 04, 1996 |
| AA | | | 500MG;7.5MG | N81080 001 AUG 30, 1991 |
| AA | | | 500MG;10MG | N40148 002 FEB 14, 1997 |
| AA | | | 650MG;7.5MG | N40094 001 SEP 29, 1995 |
| AA | | | 650MG;7.5MG | N40123 001 MAR 04, 1996 |
| AA | | | 650MG;10MG | N40094 002 SEP 29, 1995 |
| AA | | | 650MG;10MG | N40123 002 MAR 04, 1996 |
| AA | | | 750MG;7.5MG | N40122 002 MAR 04, 1996 |
| AA | | | 750MG;7.5MG | N81083 001 AUG 30, 1991 |
| AA | | ZENITH GOLDLINE | 500MG;5MG | N89696 001 APR 21, 1988 |
| | | LORTAB | | |
| AA | | MALLINCKRODT | 500MG;5MG | N87722 001 JUL 09, 1982 |
| AA | + | UCB | 500MG;10MG | N40100 001 JAN 26, 1996 |
| | | | 325MG;5MG | N40099 001 JUN 25, 1997 |
| | | NORCO | | |
| | + | WATSON LABS | 325MG;10MG | N40148 001 FEB 14, 1997 |
| | | VICODIN | | |
| AA | + | KNOLL PHARM | 500MG;5MG | N88058 001 JAN 07, 1983 |

## ACETAMINOPHEN; HYDROCODONE BITARTRATE

TABLET; ORAL
VICODIN ES

| | | | | |
|---|---|---|---|---|
| AA | + | KNOLL PHARM | 750MG;7.5MG | N89736 001 DEC 09, 1988 |
| | | VICODIN HP | | |
| AA | | KNOLL PHARM | 660MG;10MG | N40117 001 SEP 23, 1996 |

## ACETAMINOPHEN; OXYCODONE

CAPSULE; ORAL
OXYCODONE AND ACETAMINOPHEN

| | | | | |
|---|---|---|---|---|
| AA | | HALSEY | 500MG;5MG | N40219 001 JAN 22, 1998 |

## ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE

CAPSULE; ORAL
OXYCODONE AND ACETAMINOPHEN

| | | | | |
|---|---|---|---|---|
| AA | | AMIDE PHARM | 500MG;5MG | N40199 001 DEC 30, 1998 |
| AA | | MALLINCKRODT | 500MG;5MG | N40257 001 AUG 04, 1998 |
| AA | | VINTAGE PHARMS | 500MG;5MG | N40106 001 JUL 30, 1996 |
| AA | | WATSON LABS | 500MG;5MG | N40234 001 OCT 30, 1997 |
| | | ROXILOX | | |
| AA | | ROXANE | 500MG;5MG | N40061 001 JUL 03, 1995 |
| | | TYLOX | | |
| AA | + | JOHNSON RW | 500MG;5MG | N88790 001 DEC 12, 1984 |

SOLUTION; ORAL
ROXICET

| | | | | |
|---|---|---|---|---|
| | | ROXANE | 325MG/5ML;5MG/5ML | N89351 001 DEC 03, 1986 |

TABLET; ORAL
OXYCET

| | | | | |
|---|---|---|---|---|
| AA | | MALLINCKRODT | 325MG;5MG | N87463 001 DEC 07, 1983 |
| | | OXYCODONE AND ACETAMINOPHEN | | |
| AA | | DURAMED | 325MG;5MG | N40272 001 JUN 30, 1998 |

## ACETAMINOPHEN; HYDROCODONE BITARTRATE

ELIXIR; ORAL

HYDROCODONE BITARTRATE AND ACETAMINOPHEN

| | | | | |
|---|---|---|---|---|
| AA | + MIKART | 500MG/15ML;7.5MG/15ML | N81051 001 | AUG 28, 1992 |
| | | 500MG/15ML;5MG/15ML | N81226 001 | OCT 27, 1992 |
| | + | 500MG/15ML;5MG/15ML | N89557 001 | APR 29, 1992 |
| AA | PHARM ASSOC | 500MG/15ML;7.5MG/15ML | N40182 001 | MAR 13, 1998 |

TABLET; ORAL

ANEXSIA

| | | | | |
|---|---|---|---|---|
| AA | MALLINCKRODT | 500MG;5MG | N89160 001 | APR 23, 1987 |

ANEXSIA 10/660

| | | | | |
|---|---|---|---|---|
| AA | + MALLINCKRODT | 660MG;10MG | N40084 003 | JUL 29, 1996 |

ANEXSIA 7.5/650

| | | | | |
|---|---|---|---|---|
| AA | MALLINCKRODT | 650MG;7.5MG | N89725 001 | SEP 30, 1987 |

CO-GESIC

| | | | | |
|---|---|---|---|---|
| AA | SCHWARZ PHARMA | 500MG;5MG | N87757 001 | MAY 03, 1982 |

HY-PHEN

| | | | | |
|---|---|---|---|---|
| AA | ASCHER | 500MG;5MG | N87677 001 | MAY 03, 1982 |

HYDROCODONE BITARTRATE AND ACETAMINOPHEN

| | | | | |
|---|---|---|---|---|
| AA | ENDO PHARMS | 500MG;5MG | N40281 001 | SEP 30, 1998 |
| AA | | 500MG;7.5MG | N40280 001 | SEP 30, 1998 |
| AA | | 650MG;7.5MG | N40280 002 | SEP 30, 1998 |
| AA | | 650MG;10MG | N40280 003 | SEP 30, 1998 |
| AA | | 750MG;7.5MG | N40281 002 | SEP 30, 1998 |
| | | 400MG;5MG | N40288 001 | NOV 27, 1998 |
| | | 400MG;7.5MG | N40288 002 | NOV 27, 1998 |
| | | 400MG;10MG | N40288 003 | NOV 27, 1998 |
| AA | EON | 500MG;5MG | N40149 001 | JAN 27, 1997 |

## ACETAMINOPHEN; HYDROCODONE BITARTRATE

TABLET; ORAL

HYDROCODONE BITARTRATE AND ACETAMINOPHEN

| | | | | |
|---|---|---|---|---|
| AA | EON | 750MG;7.5MG | N40149 002 | JAN 27, 1997 |
| AA | HALSEY | 500MG;5MG | N40236 001 | SEP 25, 1997 |
| AA | | 650MG;7.5MG | N40240 002 | NOV 26, 1997 |
| AA | | 650MG;10MG | N40240 001 | NOV 26, 1997 |
| AA | | 750MG;7.5MG | N40236 002 | SEP 25, 1997 |
| AA | MALLINCKRODT | 500MG;5MG | N40084 002 | JUN 01, 1995 |
| AA | | 500MG;7.5MG | N40201 001 | FEB 27, 1998 |
| AA | | 500MG;10MG | N40201 002 | FEB 27, 1998 |
| AA | | 750MG;7.5MG | N40084 001 | JUN 01, 1995 |
| AA | + MIKART | 500MG;2.5MG | N89698 001 | AUG 25, 1989 |
| AA | | 500MG;5MG | N89271 001 | JUL 16, 1986 |
| AA | | 500MG;5MG | N89697 001 | JAN 28, 1992 |
| AA | + | 500MG;7.5MG | N89699 001 | AUG 25, 1989 |
| AA | + | 650MG;7.5MG | N89689 001 | JUN 29, 1988 |
| AA | + | 650MG;10MG | N81223 001 | MAY 29, 1992 |
| AA | PEACHTREE | 500MG;10MG | N40210 001 | AUG 13, 1997 |
| AA | UCB | 650MG;7.5MG | N40134 001 | NOV 21, 1996 |
| AA | VINTAGE PHARMS | 500MG;2.5MG | N40144 002 | APR 25, 1997 |
| AA | | 500MG;5MG | N89831 001 | SEP 07, 1988 |
| AA | | 500MG;5MG | N89971 001 | DEC 02, 1988 |
| AA | | 500MG;7.5MG | N40144 001 | FEB 22, 1996 |
| AA | | 650MG;7.5MG | N40155 001 | APR 14, 1997 |

ACETAMINOPHEN; CODEINE PHOSPHATE

TABLET; ORAL
TYLENOL W/ CODEINE
JOHNSON RW 325MG;15MG N85056 002
325MG;30MG N85056 003
325MG;60MG N85056 004

ACETAMINOPHEN; HYDROCODONE BITARTRATE

CAPSULE; ORAL
BANCAP HC
FOREST PHARMS 500MG;5MG N87961 001 MAR 17, 1983

CO-GESIC
CENT PHARMS 500MG;5MG N89360 001 MAR 02, 1988

TABLET; ORAL
DURADYNE DHC
FOREST PHARMS 500MG;5MG N87809 001 MAR 17, 1983

HYDROCODONE BITARTRATE AND ACETAMINOPHEN
BARR 500MG;5MG N88577 001 DEC 21, 1984

HALSEY 500MG;5MG N89554 001 JUN 12, 1987

ROSEMONT 500MG;5MG N89290 001 MAY 29, 1987

500MG;5MG N89291 001 MAY 29, 1987

NORCET
ABANA 500MG;5MG N88871 001 MAY 15, 1986

TYCOLET
JOHNSON RW 500MG;5MG N89385 001 AUG 27, 1986

VICODIN
KNOLL PHARM 500MG;5MG N85667 001

ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE

CAPSULE; ORAL
OXYCODONE AND ACETAMINOPHEN
HALSEY 500MG;5MG N89994 001 MAY 04, 1989

ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE

CAPSULE; ORAL
TYLOX-325
JOHNSON RW 325MG;5MG N88246 001 NOV 08, 1984

TABLET; ORAL
OXYCODONE 2.5/APAP 500
DUPONT MERCK 500MG;2.5MG N85910 001
OXYCODONE 5/APAP 500
DUPONT MERCK 500MG;5MG N85911 001

ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE; OXYCODONE TEREPHTHALATE

CAPSULE; ORAL
TYLOX
JOHNSON RW 500MG;4.5MG;0.38MG N85375 001

ACETAMINOPHEN; PROPOXYPHENE HYDROCHLORIDE

TABLET; ORAL
DARVOCET
LILLY 325MG;32.5MG N16844 001
DOLENE AP-65
LEDERLE 650MG;65MG N85100 001
PROPOXYPHENE HCL AND ACETAMINOPHEN
MYLAN 325MG;32MG N83689 001

ACETAMINOPHEN; PROPOXYPHENE NAPSYLATE

TABLET; ORAL
PROPOXYPHENE NAPSYLATE AND ACETAMINOPHEN
CIRCA 325MG;50MG N70398 001 DEC 18, 1986

650MG;100MG N70399 001 DEC 18, 1986

HALSEY 325MG;50MG N72105 001 MAY 13, 1988

650MG;100MG N72106 001 MAY 13, 1988

SUPERPHARM 650MG;100MG N71319 001 JAN 06, 1987

TEVA 650MG;100MG N70732 001 JAN 03, 1986

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

**Treatment:** A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac. If the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not wait acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

## DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.

## HOW SUPPLIED

Lortab 5/325 tablets (Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg/325 mg) contain hydrocodone bitartrate 5 mg (Warning: May be habit forming) and acetaminophen 325 mg. They are supplied as white with orange specks capsule-shaped, bisected tablets, debossed "Whitby/935," in containers of 100 tablets, NDC 50474-935-01, and in containers of 500 tablets, NDC 50474-935-50.

**Storage:** Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container with a child-resistant closure.

**CAUTION:** Federal law prohibits dispensing without prescription.

A Schedule CIII Narcotic.

Manufactured For:
**UCB PHARMA, INC.**
Atlanta, GA 30080

Manufactured By:
**MIKART, INC.**
Atlanta, GA 30318

Rev. 1/96
Code 667800
P/N FDA Sub.2

# LORTAB® 5/325

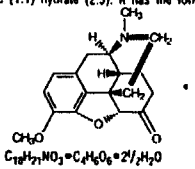
## HYDROCODONE* BITARTRATE AND ACETAMINOPHEN TABLETS, USP 5 mg/325 mg

***Warning: May be habit forming.**

## DESCRIPTION

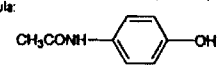
Hydrocodone bitartrate and acetaminophen is supplied in tablet form for oral administration.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2^1/_2H_2O$ MW = 494.50

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$ MW = 151.16

Each Lortab 5/325 tablet contains:

| | |
|---|---|
| Hydrocodone Bitartrate | 5 mg |
| Warning: May be habit forming | |
| Acetaminophen | 325 mg |

In addition each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized starch, stearic acid and sugar spheres which are composed of starch derived from corn, sucrose, and FD&C Yellow #6.

## CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

**Pharmacokinetics:** The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the *half-life was determined* to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and *following overdosage*. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with *small amounts of other conjugates* and unchanged drug.

See OVERDOSAGE for toxicity information.

## INDICATIONS AND USAGE

Lortab 5/325 (Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg/325 mg) are indicated for the relief of moderate to moderately severe pain.

## CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

## WARNINGS

**Respiratory Depression:** At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also *affects the center that controls respiratory rhythm*, and may produce irregular and periodic breathing.

**Head Injury and Increased Intracranial Pressure:** The respiratory depressant effects of *narcotics and their capacity* to elevate cerebrospinal fluid pressure may be *markedly exaggerated* in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with *head injuries*.

**Acute Abdominal Conditions:** The administration of *narcotics may obscure* the diagnosis or clinical course of patients with acute abdominal conditions.

## PRECAUTIONS

**General:** Special Risk Patients: As with any narcotic analgesic agent, Lortab 5/325 tablets should be *used with caution* in elderly or debilitated patients, *and those* with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough *reflex*; as *with* all narcotics, caution should be exercised when Lortab 5/325 tablets are used postoperatively and in patients with pulmonary disease.

**Information for Patients:** Hydrocodone, like all narcotics, may impair *mental and/or physical abilities required* for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, *and should be* avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

**Laboratory Tests:** *In patients with severe* hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

**Drug Interactions:** Patients receiving narcotics, *antihistamines*, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone bitartrate and acetaminophen tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO *inhibitors* or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

**Drug/Laboratory Test Interactions:** *Acetaminophen may produce* false-positive test results for urinary 5-hydroxyindoleacetic acid.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or *impairment of fertility*.

**Pregnancy:**

*Teratogenic Effects:* Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Lortab 5/325 tablets *should* be used during pregnancy only *if the potential benefit* justifies the potential risk to the fetus.

*Nonteratogenic Effects:* Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, *hyperactive reflexes*, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

**Labor and Delivery:** As *with all narcotics*, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

**Nursing Mothers:** Acetaminophen is excreted in breast *milk in small amounts*, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from *hydrocodone and acetaminophen*, a decision should be made whether to *discontinue nursing* or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

## ADVERSE REACTIONS

The most frequently reported adverse reactions are light-headedness, *dizziness*, sedation, nausea and vomiting. These effects seem to be *more prominent* in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

**Central Nervous System:** Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

**Gastrointestinal System:** Prolonged administration of Lortab 5/325 tablets may produce constipation.

**Genitourinary System:** Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported *with opiates*.

**Respiratory Depression:** Hydrocodone bitartrate may produce *dose-related respiratory* depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

**Dermatological:** Skin rash, pruritus.

The following adverse drug events may be *borne in mind* as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

## DRUG ABUSE AND DEPENDENCE

**Controlled Substance:** Lortab 5/325 tablets (Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg/325 mg) are classified as a Schedule III controlled substance.

**Abuse and Dependence:** Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which *continued administration* of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. *Tolerance*, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among *patients*.

## OVERDOSAGE

Following an acute overdosage, toxicity may *result from* hydrocodone or acetaminophen.

**Signs and Symptoms:**

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in *respiratory rate* and/or tidal volume, Cheyne-Stokes *respiration*, cyanosis) extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest *and death* may occur.

## Proposed Package Insert

# HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP

**5 mg/325 mg**

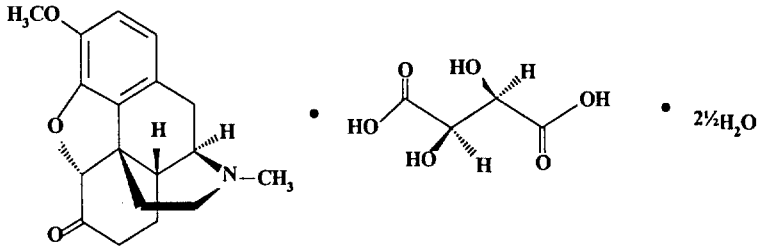
C III

**Rx only**

## DESCRIPTION

Hydrocodone Bitartrate and Acetaminophen Tablets are supplied in tablet form for oral administration.

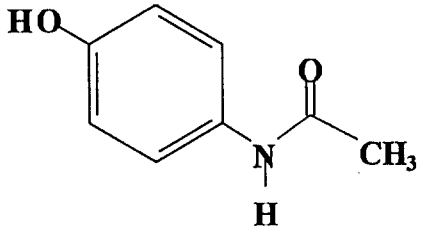
Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is: 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:




**Hydrocodone Bitartrate**

$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2½\ H_2O$ MW=494.50

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:




**Acetaminophen**

$C_8H_9NO_2$ MW = 151.17

Each HYDROCODONE BITARTRATE AND ACETAMINOPHEN, USP 5 mg/325 mg tablet contains:

Hydrocodone Bitartrate, USP. . . . . .5 mg

Acetaminophen, USP. . . . . 325 mg

In addition, each tablet contains the following inactive ingredients: Crospovidone NF, Magnesium Stearate NF, Microcrystalline Cellulose NF, Povidone USP, Pregelatinized Starch NF, Silicon Dioxide NF, and Stearic Acid NF.

## CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

**Pharmacokinetics:** The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α - and 6-β-hydroxymetabolites.

See **OVERDOSAGE** for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See **OVERDOSAGE** for toxicity information.

## INDICATIONS AND USAGE

Hydrocodone bitartrate and acetaminophen tablets are indicated for the relief of moderate to moderately severe pain.

## CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

## WARNINGS

**Respiratory Depression:** At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

**Head Injury and Increased Intracranial Pressure:** The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

**Acute Abdominal Conditions:** The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

## PRECAUTIONS

**General:** Special Risk Patients: As with any narcotic analgesic agent, hydrocodone bitartrate and acetaminophen tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when hydrocodone bitartrate and acetaminophen tablets are used postoperatively and in patients with pulmonary disease.

**Information for Patients:** Hydrocodone, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

**Laboratory Tests:** In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

**Drug Interactions:** Patients receiving narcotics, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone bitartrate and acetaminophen tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

**Drug/Laboratory Test Interactions:** Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

**Pregnancy:**

*Teratogenic Effects:* Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone bitartrate and acetaminophen tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Nonteratogenic Effects:* Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

**Labor and Delivery:** As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

**Nursing Mothers:** Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

## ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

**Central Nervous System:** Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

**Gastrointestinal System:** Prolonged administration of hydrocodone bitartrate and acetaminophen tablets may produce constipation.

**Genitourinary System:** Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

**Respiratory Depression:** Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory centers (see **OVERDOSAGE**).

**Dermatological:** Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.
Potential effects of high dosage are listed in the **OVERDOSAGE** section.

## DRUG ABUSE AND DEPENDENCE

**Controlled Substance:** Hydrocodone Bitartrate and Acetaminophen Tablets are classified as a Schedule III controlled substance.

**Abuse and Dependence:** Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

## OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

***Signs and Symptoms:***

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams.

**Treatment:** A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 grams.

## DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.

## HOW SUPPLIED

Each HYDROCODONE BITARTRATE AND ACETAMINOPHEN, USP 5 mg/325 mg tablet contains Hydrocodone Bitartrate 5 mg and Acetaminophen 325 mg. It is available as an oval-shaped white tablet debossed with M365 on one side and bisected on the other side.

Bottles of 100 .....NDC No. 0406-0365-01
Bottles of 500.....NDC No. 0406-0365-05
Bottles of 1000.....NDC No. 0406-0365-10
Unit Dose.....NDC No. 0406-0365-63

**Storage:** Store at controlled room temperature 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container with a child-resistant closure.

Mallinckrodt Inc.
St. Louis, Missouri 63134, U.S.A.

9/99

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